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The morphological ultrasound types known as ‘blob’ and ‘bagel’ signs should be reclassified from probable to definite ectopic pregnancy

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ultrasound diagnosis

ABSTRACT

OBJECTIVES: In a recent consensus statement on early pregnancy nomenclature by
Barnhart 2011, a definite ectopic pregnancy (EP) was defined morphologically on

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transvaginal ultrasound (TVS) as an extra-uterine gestational sac(GS) with yolk sac and/or embryo(with or without cardiac activity) whilst a probable EP defined as an inhomogeneous adnexal mass("blob" sign) or extra-uterine sac-like structure("bagel" sign). This study aims to determine whether the ultrasound markers used to define probable EP can be used to predict a definite tubal EP.

METHODS:Retrospective cohort study of women presenting to Early Pregnancy Unit(EPU) between January 2006 - June 2016. Women classified with a probable EP or pregnancy of unknown location (PUL),i.e. no signs of extra or intrauterine pregnancy(IUP) at the first TVS were included whilst those with a definite EP, IUP or non-tubal EP were excluded from final analysis. The gold standard for EP was histological confirmation of chorionic villi in removed fallopian tube at laparoscopy. Performances of 'probable EP' on ultrasound were evaluated in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). This was compared to the performance of 'definite EP' to predict EP.

RESULTS:During the study period 7,490 consecutive women attended the EPU. In total, 849 (240 probable EPs & 609 PULs at primary TVS) included in final analysis. 6,515 IUPs, 21 definite EPs and 48 non-tubal EPs excluded from the study. 57 women lost follow up. Probable EPs classified as either "blob" (174/240 (72.5%)) or "bagel" signs (66/240 (27.5%)). PUL final outcomes included: 47 EPs (24 blob, 19 bagel and 4 GS with embryo/yolk sac), 391 failed PULs, 143 IUPs & 28 persistent PULs. 101/198 (51%) of all "blob" sign cases and 50/85 (59%) of all "bagel" sign cases had surgery. Histology proved a tubal EP in the "blob" and "bagel" groups in 98/101 (97%) and 48/50 (96.0%), respectively. The sensitivities, specificities, PPVs, NPVs

for the “blob” and “bagel” signs were 89.9%/83.3%, 99.5%/99.6%, 97%/95% and 98.3%/98.6%, respectively. This was comparable to the presence of a definite EP on TVS (82.7%, 99.9%, 97.7% and 99.2% (p-value=0.5)).

CONCLUSIONS: “Blob” and “bagel” signs seem to be the most common presentations of an EP in ultrasound imaging. Although they cannot be considered as a definitive sign of EP, the positive predictive value is very high (>95%) and such women therefore should be considered at very high risk for having an EP and should be treated as such.

INTRODUCTION

The traditional gold standard for diagnosis of tubal ectopic pregnancies (EPs) is direct visualisation of an adnexal mass, usually at laparoscopy, followed by histological

confirmation after salpingectomy or linear salpingotomy(1-3).The introduction of high resolution transvaginal ultrasound scan (TVS) to modern practice has allowed earlier diagnosis of EP and it is now widely accepted that TVS is, arguably, the modern gold standard for diagnosing EP, both tubal and non-tubal (4).

EPs manifest in various morphological forms when assessed using ultrasound; these include visualisation of an adnexal mass which is clearly not a part of the ipsilateral ovary or a part of the uterus and appear as either an inhomogeneous mass (“blob” sign 57.9%), or can contain an empty gestational sac (“bagel” sign 20.4%) or an embryonic pole with a measurable crown rump length, with or without cardiac beat (13.2%). (4-6). Historically, in North America the most stringent sonographic criteria for the diagnosis of EP have been used to classify an EP before intervening, i.e. either a living extra-uterine pregnancy or an extra-uterine gestational sac containing yolk sac or embryo(5, 7). In 2011, these strict criteria were adopted, in a multinational consensus statement on nomenclature and definitions, to define a definite EP using TVS. It was also agreed that “bagel” or “blob” sign seen on TVS should be used when classifying a probable EP(8).

In experienced hands, the ability to diagnose EP using TVS at an earlier stage in its natural history, primarily before tubal rupture may occur, has allowed us to offer non-surgical management strategies(9,10). For this reason, final histological confirmation will not always be possible and consequently, successful treatment of EP in these women is based upon the serum human chorionic gonadotropin levels falling to an undetectable level(11-14). According to published guidelines, a live extra-uterine pregnancy(i.e. definite EP), is a contraindication to both expectant and medical management strategies(5, 15). This means that the sonographic morphological types of EP which are eligible for conservative management strategies include both the “blob”

and “bagel” signs. As per Barnhart statement (8) these are considered probable EP and therefore one can assume that EPs diagnosed with blob or bagel sign are being selected for either methotrexate injection or a ‘wait and watch’ approach. Clinician uncertainty around the interpretation of the term ‘probable EP’ on ultrasound reports has the potential to cause harm especially when administering methotrexate. In this study we aim to assess whether the probable EPs (i.e. “blob” and “bagel” sonographic signs) should be reclassified as definite EPs.

METHODS

Study design: retrospective study

Participants: Consecutive first trimester women presenting to the Early Pregnancy Unit (EPU) at Nepean Hospital, Sydney, Australia between January 2006 and June 2016 underwent TVS. Women either self-referred, were referred by their General Practitioner or the Emergency Department to the EPU.

TVS were performed by clinical fellows using a 4-9 MHz transvaginal probe (Medison X8 or Medison Accuvix V20 Prestige, Samsung Medison, Seoul, South Korea). These observers were not blinded to the clinical background or biochemical results of each woman. The TVS results were overseen by the Lead Consultant GC. Women were included in the current study if at the primary TVS either a probable EP or pregnancy of unknown location (PUL) was confirmed. Probable EPs were defined using Barnhart’s TVS consensus definition: (i) an inhomogeneous mass or “blob” sign adjacent to the ovary and moving separately to this; or (ii) a mass with a hyper-echoic ring around the gestational sac or “bagel” sign (Fig1). PUL was defined using Barnhart’s TVS definition: no signs of intra- or extra-uterine pregnancy. Eligible

women had a comprehensive history, clinical examination and quantitative human chorionic gonadotrophin (hCG) levels recorded.

Women were excluded from our study if at the primary TVS there was the presence of an IUP, definite EP or non-tubal EP. IUP was defined using Barnhart's TVS consensus definition: intra-uterine gestational sac with yolk sac and/or embryo with or without cardiac activity present. Definite EP as per Barnhart's consensus definition was extra-uterine gestational sac with yolk sac and/or embryo with or without cardiac activity. Non-tubal EP was defined as visualised ectopic mass in one of the following anatomical locations: interstitium, cervix, ovary or previous caesarean section scar (16).

Follow up in those women with a PUL was done using TVS and quantitative hCG (please see Figure 2).

The gold standard for the diagnosis of tubal EP was histopathological confirmation of chorionic villi in the removed fallopian tube (Fig 3). The pathologist was blinded to the pre-operative ultrasound findings. Those women with pre-operative diagnosis of tubal EP on TVS whose subsequent laparoscopy was negative did not undergo salpingectomy. Those women with a TVS diagnosis of an EP who were managed non-surgically were excluded from the final analysis as there was no confirmatory histology of chorionic villi within the fallopian tube. Please note that those women initially managed non-surgically who subsequently required surgery (i.e. failed conservative management), were included in the final analysis as there was histopathological confirmation of chorionic villi within the fallopian tube.

Statistical analysis

The statistical analysis was performed using IBM SPSS software version 23. The performance of the blob and bagel ultrasound signs were evaluated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-). The performance of definite EP on TVS defined as the presence of a gestational sac with yolk sac / embryo was also evaluated in terms of sensitivity, specificity, PPV, NPV, LR+ and LR-. 95% confidence intervals (CIs) were calculated. P-values < 0.05 represented statistical significance.

RESULTS

During the study period, 7,490 consecutive women attended the EPU. In total, 849 (240 probable EPs and 609 PULs at primary TVS) women were included in the final analysis. 6,515 IUPs, 21 definite EPs and 48 non-tubal EPs were excluded from the study (please see Figure 4). 57 women were lost to follow up. Probable EPs were classified as either blob (174/240 (72.5%)) or bagel signs (66/240 (27.5%)). PUL final outcomes included: 47 EPs (24 blob, 19 bagel and 4 GS with embryo/yolk sac), 391 failed PULs, 143 IUPs and 28 persistent PULs. Table 1 shows the descriptive characteristics for the study population. 101/198 (51%) of “blob” sign cases and 50/85 (59%) of “bagel” sign cases underwent surgery. The breakdown of surgical vs non-surgical management as well as the histopathology results are noted in Figure 4.

Tables 2a and 2b demonstrates the performances of the blob or bagel signs respectively on TVS to detect EP in women who underwent surgery. Table 3 demonstrates the performance of definite EP (as defined by Barnhart consensus) to

detect EP in women who underwent surgery. Please note that although the performance of definite EP on TVS to detect EP was marginally better than probable EP, this difference was not statistically significant (p -value=0.5).

Table 4 shows the details of the five cases with negative laparoscopies/histology. It is important to emphasise that in our series, none of the blob or bagel signs noted on initial scan had progressed to a viable IUP.

DISCUSSION

Our study has demonstrated that probable EPs on ultrasound, as defined by the Barnhart consensus, correlate well with subsequent histological conformation at salpingectomy. Importantly the test performance of these ultrasound markers (blob and bagel signs) for the prediction of EP were comparable to the presence of a definite EP as defined by the Barnhart consensus (gestational sac containing yolk sac and/or embryo) (p -value = 0.5).

The biggest limitation of this study is that not all women classified as probable EP were treated surgically and therefore were not subject to the same laparoscopic/histological reference standard (101/198 (51%) of “blob” sign cases and 50/85 (59%) of “bagel” sign cases underwent surgery).

We also acknowledge that not all subjects in the PUL group underwent laparoscopy. Although using this approach on all women with a PUL in this study would have ruled out the diagnosis of an EP, it is difficult to justify this on ethical grounds. Laparoscopy is invasive and not without risks. In the clinical situation where pregnant

women are not only clinically stable but also relatively asymptomatic, it is difficult to justify its use. As the vast majority of PULs are non-ectopic pregnancies(17) (18, 19) non-invasive diagnostic techniques including serum hormone measurements and TVS were used for all three groups. (1) Some of the EP group also underwent laparoscopy for treatment as well as diagnostic confirmation. Consequently, there was a bias that enters from selecting those at high risk for the more invasive test. Although laparoscopy is accepted to be the gold standard, it does have its limitations. It does not confer 100% sensitivity. Some early ongoing EPs are too small to be visualized at the time of laparoscopy, i.e. false-negative laparoscopies and a proportion of EPs are self-limiting and are never seen. (20)

The results from our study may not be generally applicable to other units. Our unit is a highly specialised centre where the ultrasound scans are performed by experienced operators, and therefore our rate of PULs (8.9%) and the rate of EPs within our PUL population (7.7%) are at the lower end of the spectrum when compared to other published units. (21) Nevertheless our results reaffirm the importance of thoroughly examining the adnexal regions not only for definite EPs but also blob or bagel signs.

We feel that the distinction between a definite and a probable EP is quite relevant, as it may have an impact on management. Women classified with a probable EP may well be more likely to undergo additional diagnostic testing in the form of endometrial curettage to rule out intrauterine chorionic villi. In the United States of America this is not an uncommon approach(7) however endometrial curettage is a procedure that carries risk of morbidity that should not be overlooked, not least the fact that potentially viable IUP can be terminated inadvertently (22). Arguably, it

could be construed that the perceived lack of certainty on diagnosis of EP at TVS when a generated report states ‘probable EP’ is one of the reasons for this practice in North America. The difference in reporting definite versus probable EP can also have an impact on research and global population health statistics. This issue was raised in the consensus statement of 2011 (8), however researchers in other parts of the world are still including tubal EP diagnosed with “blob” or “bagel” ultrasound signs as definite (4, 23-25).

The potential upgrading of blob and bagel signs to definite EP using TVS (in experienced hands) could improve interpretation of reports by clinicians at the cold face of management. This lowering of the threshold to include not only extra-uterine gestational sacs with yolk sac and/or embryo with or without cardiac activity but also more subtle morphological forms of EP at the initial TVS may also give clinicians an assertiveness to make definitive management decisions thus averting any potential delay for the woman and subsequent potential morbidity/mortality.(26) (27)

In conclusion, the “blob” and “bagel” signs are the most common presentations of an EP in ultrasound imaging, and even though they cannot be considered as a definitive sign of EP, the PPV is very high (>95%) and such women therefore should be considered at very high risk for having an EP and should be treated as such. These findings apply only to highly specialized centers with high ultrasound expertise. It must be emphasised that when a non-experienced observer misdiagnoses a corpus luteum as being a “blob” sign in a very early pregnancy, such conclusion might lead to erroneous use of methotrexate in viable IUP. Therefore concluding that “blob” and

“bagel” signs have the same value as an image of an EP with cardiac activity is still premature; further multicentre studies with larger numbers are needed.

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Figure Legends:

Figure 1: Different morphological types of ectopic pregnancy

Figure 2: PUL management flow sheet

Figure 3: Blob sign with tubal appearance at laparoscopy, histopathology confirmed ectopic pregnancy

Figure 4: Flow sheet of study population

Fig 1

Morphological types of tubal ectopic pregnancy as seen on TVS

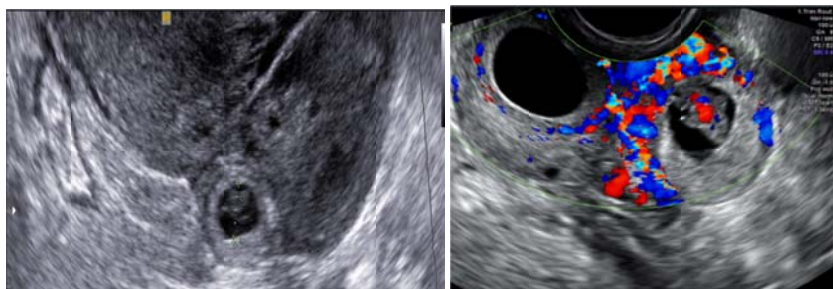
a) Probable Ectopic



1) The blob sign

2) Bagel sign

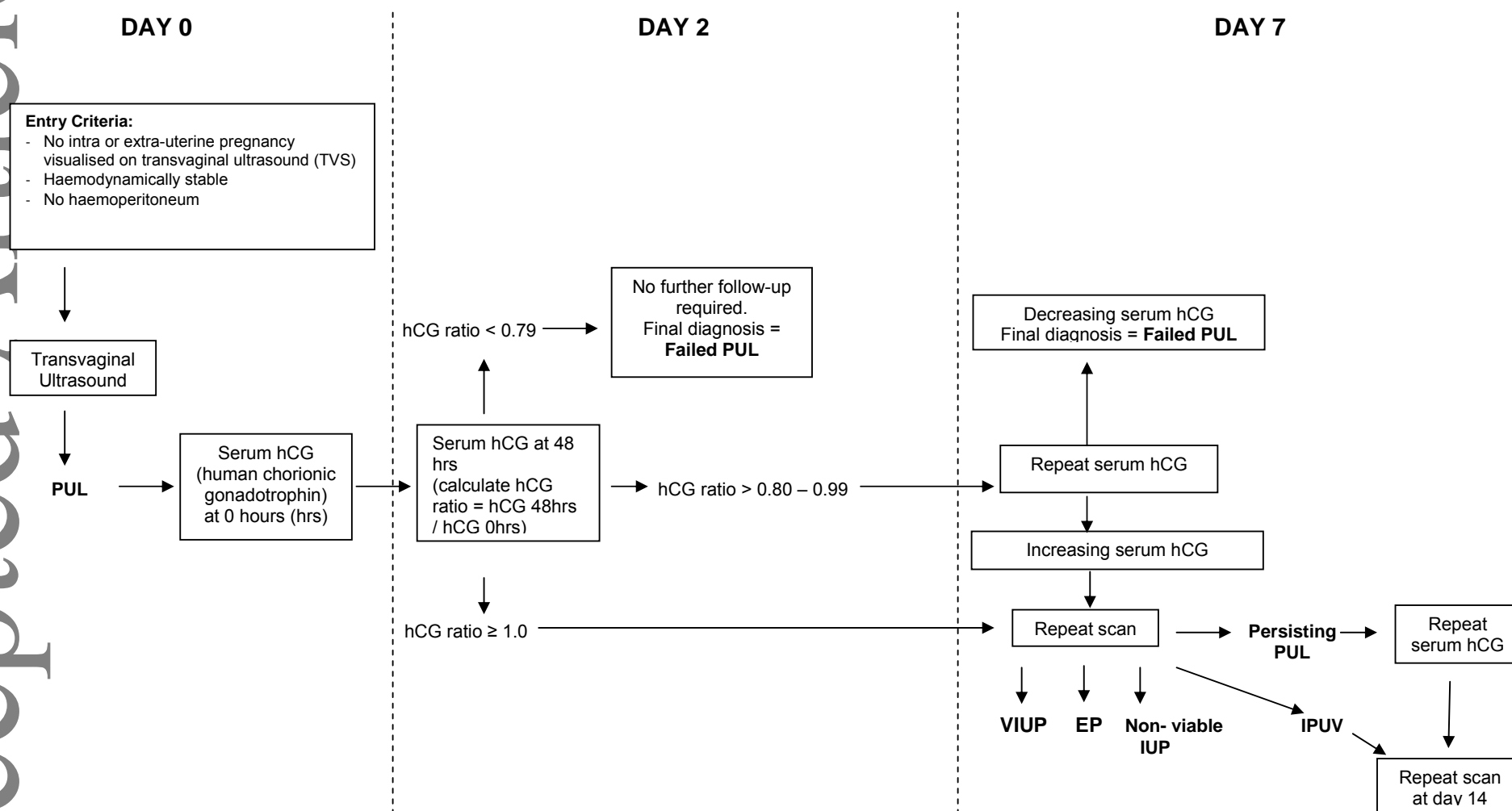
b) Definite ectopic



3) Gestational sac with
Non- viable embryo

4) Gestational sac with
embryo and cardiac activity

Fig 2 PUL management flow sheet



PUL = Pregnancy of unknown location

IPUV = Intra-uterine pregnancy of uncertain viability (= gestational sac < 25mm in diameter or an intrauterine gestational sac containing a foetal pole with CRL < 7mm with no foetal cardiac activity visualised)

VIUP = Viable intra-uterine pregnancy (= presence of embryo with visible cardiac activity)

Non-viable IUP = non-viable intra-uterine pregnancy (presence of embryo with CRL ≥ 7mm without demonstrable cardiac activity on the first scan; OR presence of an embryo with CRL ≤ 5mm with no demonstrable cardiac activity at the first scan and then at the second scan 7 days later with still no foetal cardiac activity; OR absence of an embryo in a gestational sac with a diameter of > 25 mm or a gestational sac < 25 mm with no growth at ultrasound follow-up.)

EP = ectopic pregnancy (= presence of an adnexal mass separate to the ipsilateral ovary in form of inhomogeneous mass ('blob' sign), gestational sac ('bagel' sign) or gestational sac containing embryonic pole +/- cardiac activity)

Fig 3

Blob sign with tubal appearance at laparoscopy, histopathology confirmed ectopic pregnancy

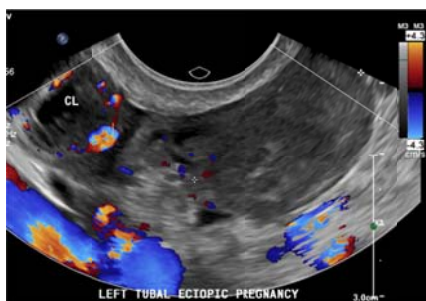
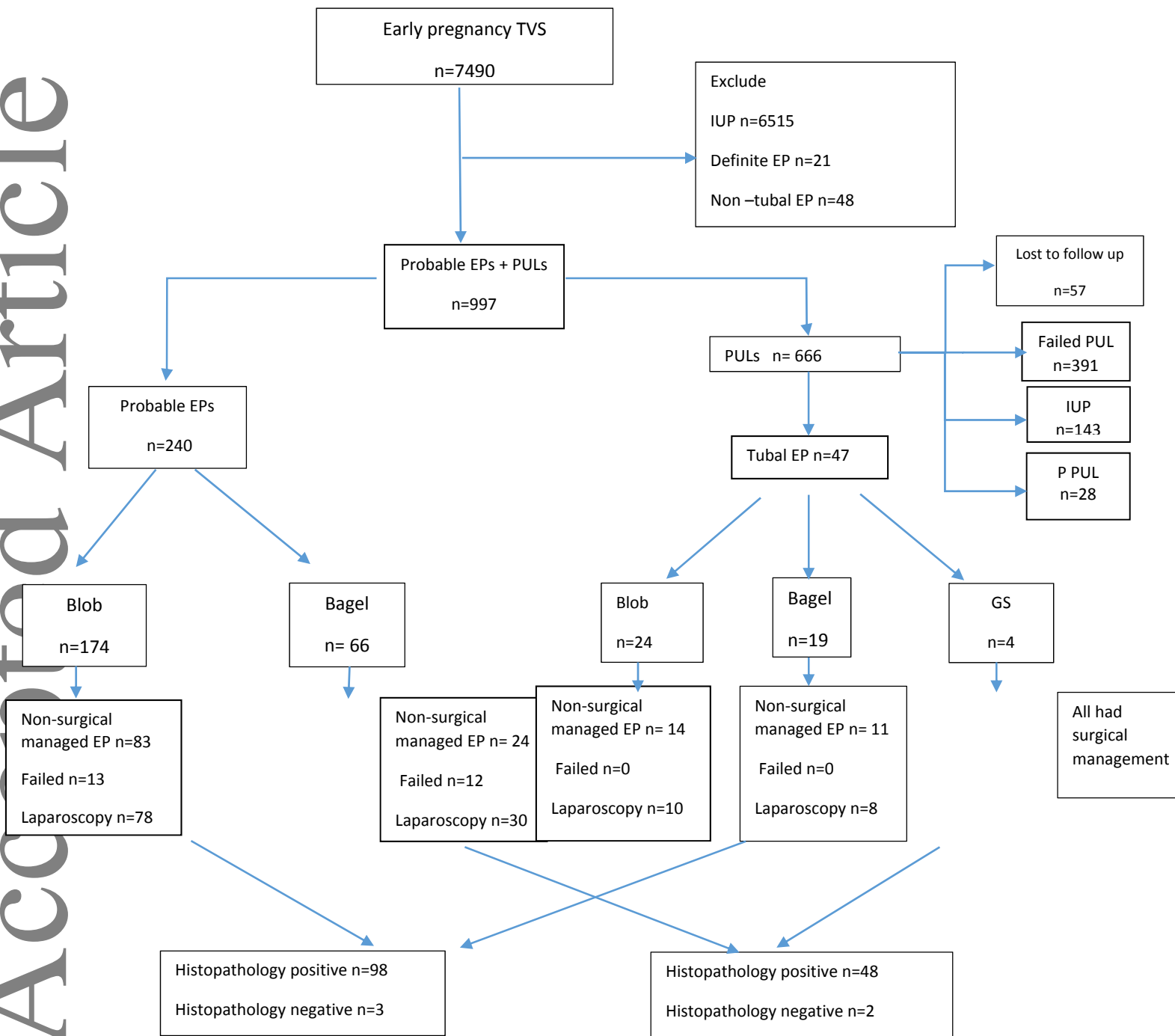


Figure 4

Flow sheet of study population



IUP = visualized intrauterine pregnancy, EP: ectopic pregnancy, PUL: pregnancy of unknown location, PPUL: persist pregnancy of unknown location

Table 1

Descriptive statistics of study population

	Probable EP on initial TVS n=240			PUL n=609					P value
	Mean± SD			Mean± SD					
	Missing	Surgical n=108	Non –surgical n=132	Missing	IUP n=143	FPUL n=391	EP n=47	PPUL n=28	
Numerical									
Maternal age(y)	0	29.7±6.3	29.2±5.9	0	27.8±6.3	30.0±7.8	30.6±5.6	29.7±4.9	0.7
Gestational age(days)	30	42.8±15.6	44.9±13.6	20	38.5±8.5	47.4±15.2	39.9±11.7	40.8±10.2	<0.5
Mean mass size(mm)	28	25.4±14.0	18.7±7.5	12	N/A	N/A	14.1±6.1	N/A	<0.5
hCG at 0 hour	19	2051.8± 2579.9	1411.3± 2461.8	7	2151.2± 10186.7	554.8± 956.9	581.2± 713.6	311.3± 401.9	<0.5
Categorical									
	n=yes			n=yes					
Parity:	0			0					
Nulliparous		34	59		61	152	13	5	<0.05
multiparous		74	73		82	239	34	23	
Previous EP	13	18	23	17	9	8	2	2	<0.05
Symptoms:									<0.05
Bleeding	7	75	96	34	53	214	36	15	
Pain	8	79	93	43	85	302	38	21	

PUL: pregnancy of unknown location

EP: Ectopic pregnancy

hCG at 0h : human chorionic gonadotrophin at presentation

SD: standard deviation

Table 2 (a)

Performance of probable EP on US to detect EP (n=101 surgically managed 'blob' sign cases)

	Histopathology confirmed ectopic		Value (CI 95%)
	Yes	No	
Blob sign	88	3	PPV = 0.97 (0.916 to 0.99)
Non EP	10	562	NPV = 0.983 (0.968 to 0.99)
Value (CI 95%)	Sensitivity 0.898 (0.822 to 0.944)	Specificity = 0.995 (0.985 to 0.998)	LR+ =169.116 (54.6 to 523.812) LR-=0.103 (0.057 to 0.185)

The true positives are those blob signs seen on TVS which were confirmed histologically following laparoscopy, the false positives were those blob signs seen on TVS which had a negative laparoscopy, the true negatives were those women who were classified as a PUL at the first scan who subsequently had a failing PUL or intra-uterine pregnancy and the false negatives were those women classified as a PUL who subsequently were shown to have a blob sign.

Table2 (b)

Performance of probable EP on US to detect EP (n= 50 surgically managed 'bagel' sign cases)

	Histopathology confirmed ectopic		Value (CI 95%)
	Yes	No	
Bagel sign	40	2	PPV= 0.952 (0.842 to 0.987)
Non EP	8	562	NPV = 0.986 (0.973 to 0.993)
Value (CI 95%)	Sensitivity 0.833 (0.704 to 0.913)	Specificity 0.996 (0.987 to 0.999)	LR+ = 235 (58.579 to 942.751) LR- = 0.167 (0.089 to 0.315)

The true positives are those bagel signs seen on TVS which were confirmed histologically following laparoscopy, the false positives were those bagel signs seen on TVS which had a negative laparoscopy, the true negatives were those women who were classified as a PUL at the first scan who subsequently had a failing PUL or intra-uterine pregnancy and the false negatives were those women classified as a PUL who subsequently were shown to have a bagel sign.

Table 3

Performance of definite EP on ultrasound to detect EP (25 surgically managed cases)

	Histopathology confirmed ectopic		Value CI 95%
	Yes	No	
Gestational sac with embryo	21	0*	PPV =0.977 [0.815 to 0.998]
Non EP	4	562	NPV= 0.992 [0.981 to 0.997]
	Sensitivity= 0.827 [0.643 to 0.927]	Specificity = 0.999 [0.992 to 1]	LR+= 930.288 [57.936 to 14937.728] LR-=0.173 [0.075 to 0.401]

*For the purpose of calculation 0.5 added to all values

EP: ectopic pregnancy

PPV: positive predictive value

NPV: negative predictive value

LR: likelihood ratio

Table 4

Details of the five cases with false positive result

	Findings at laparoscopy	Ultrasound diagnosis	hCG at 0 hour IU/L	Final diagnosis
Case one	Negative	Bagel	2231	Failed PUL
Case two	Had salpingectomy but HP negative	Bagel	1215	Failed PUL
Case three	Negative	Blob	41	Failed PUL
Case four	Negative	Blob	899	Confirmed IUP
Case five	Had salpingectomy but HP negative	Blob	2126	Confirmed IUP

HP: histopathology

PUL: pregnancy of unknown location

IUP: intrauterine pregnancy

hCG: human chorionic gonadotrophin at presentataion